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Visual System Dysfunction Following Acute Trimethyltin Exposure in Rats

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16. ABSTRACT

Trimethyltin (TMT) has been shown to produce damage in the limbic system and several other brain areas. To date, damage to sensory systems has not been reported. The present study investigated the integrity of the visual system following acute exposure to TMT. Rats were chronically implanted with electrodes for recording the evoked response from either the visual cortex or optic tract following photic stimulation. Following recovery, the animals were exposed to either 0 (saline), 4, 5, 6, or 7 mg/kg trimethyltin chloride (TMT). Evoked potentials were averaged and peak-to-peak amplitudes and latencies were determined. The results indicated that exposure to TMT produces alterations in the visual evoked response. The pattern changes suggested two effects, an alteration in tetinal processing and an alteration in arousal. The manifestation of these changes was an increase in early peak latencies recorded from the visual cortex and the optic tract, a decreased amplitude recorded from the visual cortex and optic tract early peaks (all suggestive of retinal changes) and a decreased P3N3 amplitude and N3 latency recorded from the visual cortex (suggestive of increased arousal). The results demonstrate that TMT does produce alterations in sensory systems as well as in the limbic system.

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Visual System Dysfunction Following Acute Trimethyltin Exposure in Rats[1]

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DYER, R. S., W. E. HOWELL AND W. F. WONDERLIN. *Visual system dysfunction following acute trimethyltin exposure in rats*. NEUROBEHAV. TOXICOL. TERATOL. 4(2) 191–195, 1982.—Trimethyltin (TMT) has been shown to produce damage in the limbic system and several other brain areas. To date, damage to sensory systems has not been reported. The present study investigated the integrity of the visual system following acute exposure to TMT. Rats were chronically implanted with electrodes for recording the evoked response from either the visual cortex or optic tract following photic stimulation. Following recovery, the animals were exposed to either 0 (saline), 4, 5, 6, or 7 mg/kg trimethyltin chloride (TMT). Evoked potentials were averaged and peak-to-peak amplitudes and latencies were determined. The results indicated that exposure to TMT produced alterations in the visual evoked response. The pattern of changes suggested two effects, an alteration in retinal processing and an alteration in arousal. The manifestation of these changes was an increase in early peak latencies recorded from the visual cortex and the optic tract, a decreased amplitude recorded from the visual cortex and optic tract early peaks (all suggestive of retinal changes) and a decreased P3N3 amplitude and N3 latency recorded from the visual cortex (suggestive of increased arousal). The results demonstrate that TMT does produce alterations in sensory systems as well as in the limbic system.

Visual evoked response Optic tract Trimethyltin Visual cortex Visual toxicity

TRIMETHYLTIN (TMT) has been reported to produce a pattern of neuronal degeneration which is largely restricted to the limbic system [2]. Intraventricular application of kainic acid produces a pattern of damage similar to that produced by systemic TMT administration [15]. Thus, local administration of kainic acid mimics systemic TMT administration. In addition to the hippocampal pathology produced by kainic acid following intraventricular administration, retinal damage has been described following injection of kainic acid into the vitreous humour [12,13]. Therefore, if the parallel between local kainic acid and systemic TMT is maintained, then systemically administered TMT may produce retinal damage which has not yet been detected.

Neuropathological findings do not lead one to suspect that the visual system would be affected by TMT. However, TMT has been shown to produce both aggressive behavior [2,9] and hyperactivity [16]. Impaired vision is one of many factors which may account for these two types of behavior [10,11]. One method by which visual system dysfunction may be ruled out as contributing to these abnormal behaviors is to demonstrate the functional integrity of the system by using the visual evoked response (VER).

A variety of studies have suggested that the VER technique may be used as a means to detect general CNS dysfunction as well as specific damage to the visual system (e.g., [4]). Evaluation of the VER in TMT-exposed animals would allow a partial test of that hypothesis. Finally, the late peak of the VER (i.e., P3N3) has been assumed to correlate inversely with arousal [1,4]. If this is true, it would be expected that the hyperactive and hyperreactive TMT-treated rats would have low amplitude P3N3 amplitudes.

Thus, there are a variety of reasons why TMT might be expected to produce alterations in the VER. The present study was designed to determine whether any such alterations occurred.

METHOD

Adult male Long-Evans hooded rats (n=108) were obtained from Charles River Breeding Company and housed singly in plastic cages on woodchip bedding. Access to food and water was ad lib throughout the experiment. At 60 days of age, under 3.7 ml/kg Chloropent (Fort Dodge Laboratories, Inc.) anesthesia, the rats were surgically implanted with electrodes for recording from the optic tract and/or the visual cortex. The electrodes for cortical recordings were stainless steel screws (00–90×1/16″) threaded into the skull 5 mm anterior to bregma and 2 mm lateral for ground (left side) and reference (right side). The visual cortex electrode was a screw placed 6 mm posterior to bregma and 3 mm lateral to

[1]This manuscript has been reviewed by the Health Effects Research Laboratory, U. S. Environmental Protection Agency, and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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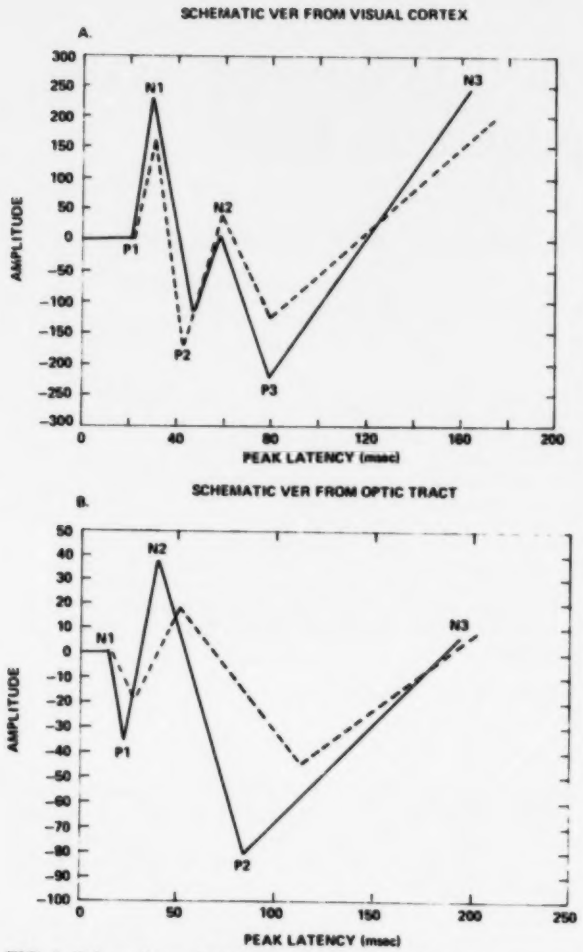

FIG. 1. Schematic evoked potentials indicating the peaks measured in this study. A: Schematic VER recorded from the visual cortex of a rat. B. Schematic VER recorded from the optic tract of a rat. Amplitudes are in arbitrary units. Dashed lines represent the changes induced by TMT.

the midline. The optic tract electrode consisted of a twisted pair of 0.25 mm nichrome wires insulated except at the tip. Coordinates for these depth placements were (with the incisors 5.0 mm above the interaural line) 0.5 mm posterior to bregma, 3.0 mm lateral and 8.1–8.8 mm below the cortical surface. If the electrode struck the base of the skull during surgery, it was raised 0.15 mm. Following placement, all electrodes were connected to an Amphenol receptacle which was subsequently cemented to the skull with dental acrylic. Following surgery, each animal received 100,000 units Penicillin G (IM).

At the beginning of each test session, a drop of 1% atropine was placed in each animal's eyes 30 minutes prior to VER testing in order to dilate the pupils. At the time of testing, the animal's head plugs were connected to the recording amplifier (low and high filters set at 0.8 Hz and 1 kHz) by a cable and placed in a small chamber with mirrors on three walls and a Grass strobe lamp on the fourth wall [5]. During each test session, the evoked response to 64 consecutive flashes of the 10 μsec strobe was averaged. Flashes were presented at 0.5 Hz, and the flash intensity was estimated by an EG&G photometer to have a peak power of 4.53×10^7 lux above background in the center of the recording chamber (intensity 16 on the Grass strobe).

The epoch duration was 409.6 msec, and samples were taken every 0.4 msec. The evoked potential averages were obtained using a Nicolet computer from which X-Y plots were obtained along with digital readouts of peak amplitudes and latencies. Latencies of VER peaks P1, N1, P2, N2, P3, and N3 were obtained. Peak-to-peak amplitudes of P1N1, N1P2, P2N2, N2P3, and P3N3 were also obtained.

Peak designations from optic tract recordings have been less standardized than VER's from the cortex. In this study, the first three positive and negative peaks were analyzed, using the same procedures described above. Figure 1 illustrates schematic averaged evoked potentials obtained from the visual cortex and optic tract.

In the first study, animals were treated with either 0 (saline vehicle) (n=10), 5 (n=10), 6 (n=9), or 7 (n=13) mg/kg trimethyltin chloride (ICN Pharmaceuticals, Plainview, New York) by gavage in a volume of 1 ml/kg, and recordings were obtained from their visual cortex, as described above, on days 1, 4, 8, and 16 following treatment. In the second study, animals were treated with either 0 (saline vehicle, n=16), 4 (n=16), 5 (n=16), or 6 (n=16) mg/kg TMT by gavage in a volume of 1 ml/kg, and recordings were obtained from both the visual cortex and the optic tract on day 0 (immediately prior to treatment), day 1, and day 4. Thus, the main differences between the first and second studies were that in the second study, a low dosage (4 mg/kg) was substituted for the high dosage (7 mg/kg); days 8 and 16 were eliminated; day 0 was included; and recordings were obtained from both cortex and optic tract.

Data from these studies were analyzed by multivariate analysis of variance (MANOVA) techniques. For each experiment, MANOVAs were performed for amplitude and latency measurements and, in the second experiment, separate MANOVAs were performed upon the optic tract and cortical recordings. MANOVAs which were significant after Bonferroni corrections were followed by ANOVAs which in turn were followed by Duncan's multiple range test for individual comparisons. The overall alpha for the experiment was thus maintained at 0.05. In addition to the overall analysis performed upon the data obtained from the visual cortex in the second experiment, planned comparisons (using Duncan's multiple range test) were made between the different dosage groups for the variables which were statistically significant in the first study.

Following these studies, all animals with optic tract electrodes were perfused with potassium ferrocyanide in Formalin, a 1.0 mA 5 sec pulse was passed through each electrode tip to aid in electrode tip localization, and the electrodes and brains were removed. Cresyl violet-stained sections were used to confirm electrode localization.

RESULTS

TMT produced increases in early peak latencies of the evoked potentials recorded from both the optic tract and the visual cortex. In addition, early peak amplitudes were depressed in both locations, and the P3N3 amplitude was depressed in the visual cortex.

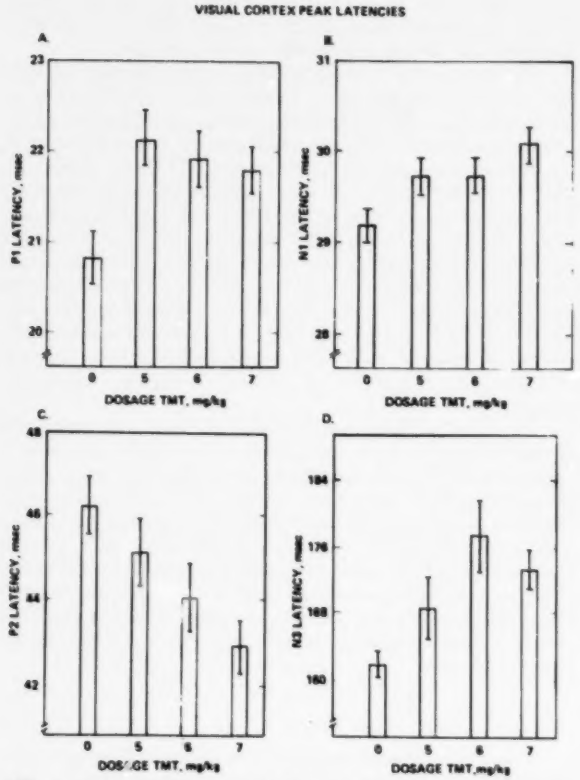

FIG. 2. Effects of TMT on peak latencies recorded from the visual cortex. A: P1 latency; B: N1 latency; C: P2 latency; and D: N3 latency. In this and other figures, the vertical lines represent +SEM.

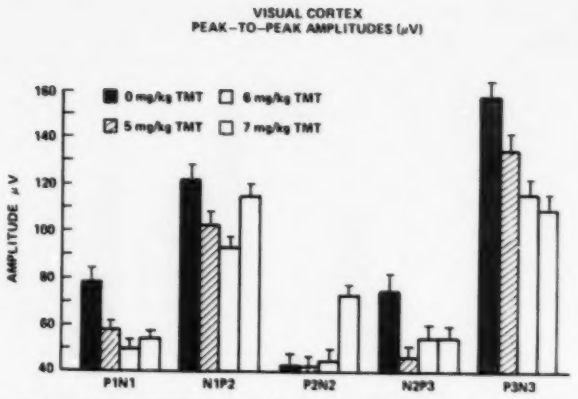

FIG. 3. Effects of TMT on peak-to-peak amplitudes recorded from the visual cortex.

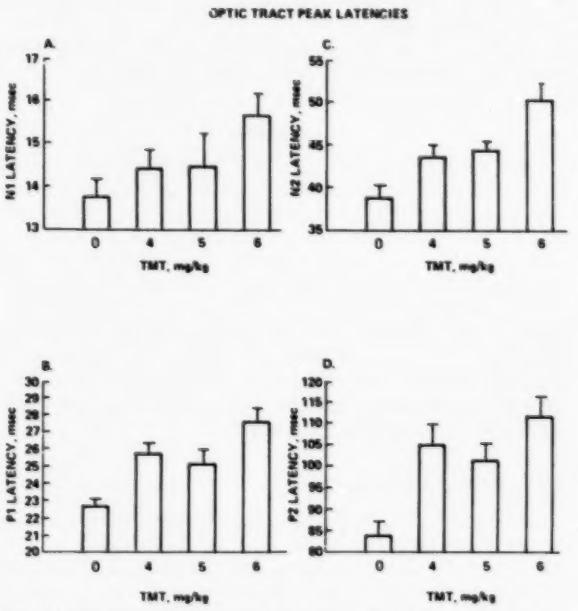

FIG. 4. Effects of TMT on peak latencies recorded from the optic tract. A: N1 latencies; B: P1 latencies; C: N2 latencies; and D: P2 latencies.

The main effects of TMT on VER latencies in the first study are illustrated in Fig. 2. TMT increased P1 and N3 latencies, but shortened P2 latencies, all F's (3,152)>3.74, p's<0.01. There were no other significant TMT-induced changes in VER latency. There were also no significant effects of day of testing, nor were there any significant treatment × day interactions. Thus, the statistics indicate that the effects of TMT upon P1, N3, and P2 latencies were present at the first post-treatment test and remained for the entire 16-day period of the experiment.

The main effects of TMT on VER amplitudes in the first study are illustrated in Fig. 3. TMT significantly decreased the amplitude of the P1N1, N2P3, and P3N3 peaks, and significantly increased the amplitude of the P2N2 peak, all F's (3,152)>4.59, p's<0.0044. Differences between the 0 (control) and low dose (5 mg/kg) groups were significant for the P1N1, N2P3, and P3N3 amplitudes and for the P1 latencies. The dose-dependent effects described above were supported by an overall significant MANOVA, F(33,149)=4.73, p<0.0001.

In the second study, the results obtained from recordings of the optic tract indicated that alterations in amplitude and latency of response could be obtained at this early level of visual processing. All amplitudes were decreased in TMT-treated rats, F's (3,179)>4.87, p's<0.003, and latencies of the N1, N2, and P2 peaks were all significantly increased, F's (3,179)>7.68, p<0.0001. Duncan's multiple range test indicated that differences between the 0 (control) and low dose (4 mg/kg) groups were significant for the N1P1, P1N2, and N2P2 amplitudes and for the N1, N2, and P2 latencies. These results (Figs. 4 and 5) were supported by an overall significant MANOVA for dose, F(27,500)=3.64, p<0.0001. In contrast to the first study, the MANOVA for the cortical recordings was not statistically significant. The planned comparisons indicated that only the P2 latency differed significantly among the different dosage groups. As with the first study, P2 latencies were shorter in treated animals than controls,

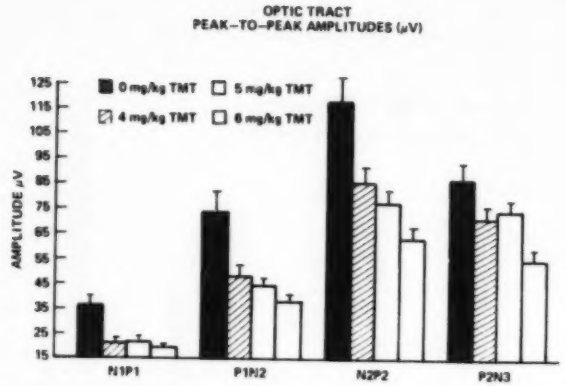

FIG. 5. Effects of TMT on peak-to-peak amplitudes recorded from the optic tract.

although the only significant difference was between the 0 and 6 mg/kg groups.

Analysis of the histological data indicated that all electrodes were accurately placed in the optic tract.

DISCUSSION

The results indicate that TMT produces visual system dysfunction. This dysfunction is characterized by a reduction in amplitude of the retinal input to the rest of the brain and by a delayed onset (i.e., increased latencies) of the response. While the changes observed were significant, the presence of an easily recognizable VER indicates that the rats were definitely not blind. The pattern of change in the cortical VER was different from changes observed following exposure to other toxicants and drugs. For purposes of analysis, the effects may be divided into two parts: the effects on early components and the effects upon the late (P3N3 amplitude, N3 latency) component.

Early VER Peak Alterations

Alterations in early peaks of the cortical VER are usually assumed to reflect abnormal input to the cortex [3,7]. The present study supports such an interpretation, because similar alterations were obtained from the optic tract. Increased cortical latencies may reflect either slowed conduction in the optic tract and optic radiations or slowed synaptic activity in the retina or lateral geniculate nucleus. If decreased conduction velocity has occurred, then the magnitude of the increased latencies should be greater in the cortex than in the optic tract, by virtue of the greater distance from the retina to the visual cortex. Similarly, if the decrement has occurred in either the lateral geniculate or the optic radiations, then the increased latencies should be greater in the cortex than in the optic tract. In the present study, the optic tract recordings were most sensitive to the disrupting effects of TMT (i.e., changes were observed at a lower dosage level). Furthermore, the magnitude of change (in msec) was at least as great, and in some cases greater in the high dose optic tract recordings than in the corresponding cortical recordings. Thus, the alterations in the early peaks of the cortical VER are probably due to changes in retinal function.

The decreased P2 latencies observed in the cortical VER do not contradict the above interpretation. If the first wave of the cortical VER (P1N1P2) is viewed as a Gaussian distribution (over time) of inputs to the cortex, then a nonspecific reduction (i.e., randomly distributed) of input would (1) lower the amplitude of the wave; and (2) move the tails of the distribution towards the mean. Thus, P1N1 and N1P2 amplitudes should be reduced, P1 latencies should be increased, P2 latencies should be decreased, and N1 latencies should stay about the same. Therefore, a general reduction in cortical input may explain the changes observed in the first part of the VER. It is not clear why the increased latencies observed at the optic tract are not reflected at the cortical level. Perhaps the variability of cortical responses masks the changes.

A variety of other procedures, including acute exposures to triethyltin [6], both acute adult and prenatal exposure to carbon monoxide [4], depletion of dopamine [7], and reduced flash intensity [8] have been found to produce alterations in the first wave of the cortical VER. None of these procedures duplicate the pattern of changes observed in the first wave following TMT exposure. Although the present study cannot indicate by what mechanism the changes have occurred, it must be assumed that the mechanism is different from the mechanism by which the other alterations mentioned above have occurred.

Late VER Peak Alterations

The TMT-induced alterations in the late VER peak may be explained in terms of the presumed relationship between this wave and arousal. Several studies have indicated that the P3N3 wave is largest in a relaxed, wakeful subject, and smallest in an aroused subject [1, 7, 14]. TMT-treated rats have been described as hyperactive, hyperrreactive, and aggressive [2, 9, 16]. Therefore, the P3N3 amplitudes should be smaller than controls in these rats and, in fact, the data indicate that the amplitudes are smaller in treated rats. These data support the hypothesis that P3N3 amplitudes are inversely correlated with arousal, and that TMT-treated rats have high arousal states.

In summary, the present experiment has described alterations in the visual system following acute exposure to TMT. The alterations are best characterized as reduced retinal output and increased cortical arousal, a pattern of changes not observed following exposure to other environmental conditions. The apparent "all-or-nothing" character of the changes in P1 latency and P1N1 amplitude suggests that exposure to lower concentrations of TMT than those used here may also produce changes in these measures.

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